Treating Sleep as a Geriatric Syndrome: Nocturia

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Syndrome:

“Symptoms and signs…which may be the final pathway of a wide range of pathophysiological alterations…
Definition of Nocturia

• Nocturia defined by International Continence Society (ICS) as:

  "the complaint that the individual has to wake at night one or more times to void … each void is preceded and followed by sleep"

Defining Nocturia: It Gets Complicated

Nocturia (ICS 2002):

The complaint that the individual has to wake at night one or more times to void, each void is preceded and followed by sleep

Nocturia (current thinking):

- Need to intervene? “Bother” vs sleep disruption
- How many voids (>1, > 2, > 3, etc)?
- Pathophysiology of sleep disruption (sleep apnea)?
- Reason for awakening (chicken vs egg)?
- Shiftwork (“nocturia” as a misnomer)
Should Bother Dictate Treatment?
Nocturia ≠ Bother

Selected AUA-7 items in relation to sleep diaries

Nocturia Frequency Does Not Always Equate With Bother to Patients

- Patients with nocturia who report high levels of bother are significantly more likely to have difficulty initiating sleep, difficulty returning to sleep, and greater morning fatigue.

<table>
<thead>
<tr>
<th>Sleep Characteristic</th>
<th>High Bother(^a)</th>
<th>Low Bother(^a)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep duration, min</td>
<td>n = 8</td>
<td>n = 12</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>380.0 ± 90.1</td>
<td>425.0 ± 80.7</td>
<td></td>
</tr>
<tr>
<td>Time to initiate sleep, min</td>
<td>n = 11</td>
<td>n = 13</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>47.7 ± 34.4</td>
<td>23.5 ± 13.6</td>
<td></td>
</tr>
<tr>
<td>Time to return to sleep, min</td>
<td>n = 10</td>
<td>n = 12</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>28.9 ± 16.1</td>
<td>15.4 ± 9.6</td>
<td></td>
</tr>
<tr>
<td>Morning fatigue(^b)</td>
<td>n = 11</td>
<td>n = 13</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>3.3 ± 0.7</td>
<td>2.5 ± 1.0</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Mean ± standard deviation.

\(^b\)Subjective morning fatigue and sleep ratings: higher scores = worse fatigue or sleep characteristics; scores range from 1 to 7.

Nocturia Is a Widely Reported Cause of Poor Sleep

Prevalence of poor sleep in 3669 Swedish women aged 40 to 64 years according to nocturia severity

From: Asplund & Aberg, Maturitas 1996:24,73-81
Nocturia Is the Leading Cause of Sleep Disturbance in Older Adults


How often do the following disturb your sleep?

<table>
<thead>
<tr>
<th>Frequency of Disturbed Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every night/almost every night</td>
</tr>
<tr>
<td>Few nights/wk</td>
</tr>
<tr>
<td>Few nights/mo</td>
</tr>
<tr>
<td>Rarely</td>
</tr>
<tr>
<td>Never</td>
</tr>
</tbody>
</table>

N = 1424; aged 55-84 years

- Nocturia
- Physical pain
- Caregiving
- Health concerns
- Cough
- Money problems
- Family problems
- Uncomfortable bed
- Headache
- Nighttime heartburn
SWS May Be Interrupted by Nocturia

The first nocturia episode occurs within 2 to 3 hours on average.
Frequency Distribution of Time to First Void (also called First Uninterrupted Sleep Period, FUSP) in Untreated Nocturia

Polysomnographic Comparison of Nocturia Patients with 1-2 Voids vs 3-4 Voids on Lab Night: All Patients with AHI < 5.0

(Bliwise, Dijk, Juul. *Neurourol Urodyn* 2015; 34: 392)
Outcomes of Nocturia
Nocturia Predicts Fall-related Fractures and Mortality in the Elderly

**Fracture Incidence**

- Fall-related fractures: 2.6% for non-nocturia patients, 5.8% for nocturia patients (p<0.03)
- All fractures: 3.5% for non-nocturia patients, 7.2% for nocturia patients (p<0.03)

**Mortality**

- Kaplan-Meier estimates show significantly lower mortality in patients without nocturia than patients with nocturia (log rank test p=0.0015); CI, confidence interval (Nakagawa H et al. *J Urol* 2010;184:1413–1418)
Nocturia and/or Urge Incontinence Increase Risk for Falls

**Nocturia**

**Urge Incontinence**
Poor Sleep Quality or Short Sleep Duration Associated with Falls Independently of Sedative/Hypnotics

- Stone et al, *Arch Inter Med* 2008; 168: 1768-75
Nocturia and Increased Risk for Depression: BACH Survey Results

Nocturia Associated with Significantly Lower Scores on 14/15 Dimensions of HRQoL

n=1,888 Finnish women (similar results in males)

*P<0.05; **P<0.001 (test for trend)

# Nocturia and Sleep Disordered Breathing in a Community-Dwelling Elderly Population

<table>
<thead>
<tr>
<th>RDI Level</th>
<th>0-9 (n=26)</th>
<th>10-24 (n=21)</th>
<th>25+ (n=11)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>76.9 (6.0)</td>
<td>79.7 (6.9)</td>
<td>76.5 (7.2)</td>
<td>.26</td>
</tr>
<tr>
<td>BMI</td>
<td>24.5 (3.8)</td>
<td>23.4 (3.0)</td>
<td>28.0 (5.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Mean Arterial Pressure</td>
<td>99.9 (11.5)</td>
<td>91.9 (11.3)</td>
<td>105.2 (14.7)</td>
<td>.015</td>
</tr>
<tr>
<td># NOC Voids (3-day voiding diary)</td>
<td>1.7 (1.1)</td>
<td>1.6 (0.9)</td>
<td>2.6 (1.4)</td>
<td>.028</td>
</tr>
</tbody>
</table>

Note: Subjects with CHF, uncontrolled diabetes and men with post-void residual volumes > 100 cc excluded; loop diuretics excluded.

From: Endeshaw et al, JAGS 2004; 52: 957-60
Polysomnographic (PSG) Measures and Nocturia
Sleep Heart Health Study (n = 6342)

*NOTES: Nocturia defined as *at least 1* awakening to use the bathroom ≥ 5 nts/month; Values represent median (IQR) or %’s


<table>
<thead>
<tr>
<th>PSG Measure</th>
<th>Nocturia</th>
<th>No Nocturia</th>
<th>Comparison (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Duration</td>
<td>365 (317, 404)</td>
<td>367 (322, 408)</td>
<td>.06</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>82.8 (75.4, 88.0)</td>
<td>85.1 (77.4, 90.1)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>WASO</td>
<td>55.5 (34.0, 87.0)</td>
<td>43.5 (26.5, 76.5)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>N1%</td>
<td>4.6 (2.8, 7.2)</td>
<td>4.5 (2.8, 7.1)</td>
<td>.32</td>
</tr>
<tr>
<td>N2%</td>
<td>57.5 (49.3, 65.4)</td>
<td>57.2 (49.3, 64.9)</td>
<td>.30</td>
</tr>
<tr>
<td>N3%</td>
<td>16.7 (8.2, 25.7)</td>
<td>17.0 (8.2, 24.6)</td>
<td>.36</td>
</tr>
<tr>
<td>REM%</td>
<td>19.8 (15.4, 23.7)</td>
<td>20.5 (16.5, 24.3)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>AHI &gt; 15 (%)</td>
<td>23.2</td>
<td>17.4</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
Nocturia Episodes Reduced by CPAP

No Effect of CPAP on Nocturia

The PREDICT Trial

Chicken and Egg

• Do patients awaken because of the need to void?  OR…

• Do patients awaken from other causes and then appreciate bladder sensations that prompt the bathroom trip?
Nocturia in the Sleep Lab

*Only half of 121 awakenings to void attributed to urinary urgency*

Bidirectionality in a Longitudinal Study of Nocturia and Poor Sleep

5-year follow up of the BACH Cohort

(Araujo et al, *J Urol* 2014; 191: 100-6)

Controlling for baseline sleep (or nocturia) and controlling for age, sex, race, SES, diabetes, heart disease, alcohol, physical Activity, smoking, anti-depressants, sedative/hypnotics, stimulants

MULTIVARIATE ODDS RATIO (95% CI)

- OR = 1.42
- OR = 1.98
Attributable Fraction (%) of Nocturia Cases Eliminated If Exposure was Eliminated (Finland Study): Snoring Awakening Because of Urge vs. Voiding When Awake

Attributable Fraction (%) of Nocturia Cases Eliminated If Exposure was Eliminated (Finland Study): Restless Legs Awakening Because of Urge vs. Voiding When Awake

Urgency: Danish Symptom Score

RLS (Restless Legs Syndrome): Nordic Sleep Questionnaire

Detrusor Overactivity (DO) during Sleep in Patients with Overactive Bladder (OAB)

7 of 9 OAB pts also had nocturnal polyuria; control groups show neither DO nor NP

DO defined as pressure of ≥ 2 cm H20 for ≥ 1 sec

(Pdet: detrusor pressure (Pves – Pabd))

(Krystal et al, *J Urol* 2010; 184: 623-8)
Sleep Apnea and Incontinence in the Nursing Home

Wetness Episodes Can Begin During Apneic Events

TREATMENTS
TURP has Limited Effect on Nocturia

- 118/138 (85.5%) BPO patients had nocturia before TURP
- After treatment, 91 of these (77.1%) still reported nocturia
- Improvement in nocturia score (1.0) significantly inferior to improvements for all other IPSS symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients scoring ≥2 score before TURP</th>
<th>Patients scoring ≥2 score after TURP</th>
<th>Rate of response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emptying</td>
<td>102</td>
<td>27</td>
<td>54.3</td>
</tr>
<tr>
<td>Voiding frequency</td>
<td>116</td>
<td>63</td>
<td>38.4</td>
</tr>
<tr>
<td>Intermittency</td>
<td>101</td>
<td>33</td>
<td>49.3</td>
</tr>
<tr>
<td>Urgency</td>
<td>103</td>
<td>70</td>
<td>37.0</td>
</tr>
<tr>
<td>Weak stream</td>
<td>122</td>
<td>35</td>
<td>63.0</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>84</td>
<td>18</td>
<td>47.8</td>
</tr>
<tr>
<td>Nocturia</td>
<td>118</td>
<td>91</td>
<td>19.6</td>
</tr>
</tbody>
</table>

TURP not the answer – are other mechanisms involved?

GABAergic Medication May Enhance Efficacy of Nocturia Rx
Additive Effects of Zolpidem + α Blocker

Song & Ku, Int Urol Nephrol 2007; 39: 1147-52
Can Treating Insomnia Behaviorally Benefit Nocturia in the Elderly?

*Brief Behavioral Treatment for Insomnia (BBTI) vs Information Control (IC)*


![Graph showing comparison between BBTI and IC for total nocturnal voids and PSQI Global Score over baseline and post-treatment periods.](image-url)
Solifenacin-related Improvements in Sleep Quality: Assessment with Wrist Actigraphy

*Open label, single-group design of a muscarinic antagonist*  

<table>
<thead>
<tr>
<th></th>
<th>BASELINE</th>
<th>8 WEEKS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLEEP LATENCY (mins)</strong></td>
<td>13.8 (13.9)</td>
<td>13.1 (10.8)</td>
<td>.683</td>
</tr>
<tr>
<td><strong>TOTAL SLEEP TIME (mins)</strong></td>
<td>352.2 (46.4)</td>
<td>368.8 (44.4)</td>
<td>.030</td>
</tr>
<tr>
<td><strong>SLEEP EFFICIENCY (%)</strong></td>
<td>73.0 (7.2)</td>
<td>75.7 (6.2)</td>
<td>.007</td>
</tr>
<tr>
<td><strong>WAKE AFTER SLEEP ONSET (mins)</strong></td>
<td>98.0 (40.0)</td>
<td>89.6 (35.5)</td>
<td>.096</td>
</tr>
<tr>
<td><strong>NUMBER OF AWAKENINGS</strong></td>
<td>30.8 (7.7)</td>
<td>29.6 (7.7)</td>
<td>.272</td>
</tr>
</tbody>
</table>
“...this study and others show that **NP** (nightly urine overproduction) is present in most patients with **nocturia**, including those with persistent nocturia despite **BPH** and **OAB** therapy. This finding is consistent regardless of gender, age and ethnicity.”

Age Differences in Urine Production during the Constant Routine

Controlling for fluid and food intake, posture, sleep and lighting

Black line = younger (X age = 26)
Red line = older (X age = 69)
Increase in FUSP With Desmopressin Melt (50 µg) in Men Over 3 Months’ Nightly Administration

Improvement in Nocturia is Associated with Improvements in Sleep Quality

One hour increase in FUSP was associated with a significant improvement in 7 out of 8 components of the PSQI

<table>
<thead>
<tr>
<th>PSQI Scale Component</th>
<th>n</th>
<th>Parameter estimate</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>607</td>
<td>-0.488</td>
<td>0.054</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>633</td>
<td>-0.106</td>
<td>0.012</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Latency</td>
<td>609</td>
<td>-0.079</td>
<td>0.015</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>632</td>
<td>-0.068</td>
<td>0.013</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>632</td>
<td>-0.102</td>
<td>0.018</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>634</td>
<td>-0.044</td>
<td>0.012</td>
<td>=0.0002</td>
</tr>
<tr>
<td>Sleep Medication</td>
<td>634</td>
<td>-0.016</td>
<td>0.016</td>
<td>=0.30</td>
</tr>
<tr>
<td>Daytime Dysfunction</td>
<td>634</td>
<td>-0.075</td>
<td>0.014</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Bliwise et al, *Sleep Medicine* 2014; 15: 1276-8
Lengthening of FUSP in Nocturia Increases the Odds of a Longer Total Sleep Duration

(Bliwise et al, *Sleep Health* 2015; 1: 211-3)
Conclusions

• Nocturia most assuredly meets criteria for a syndrome, particularly important for geriatrics

• It is associated with many morbidities (symptoms and signs), none the least of which is poor sleep itself

• Knowledge of successful treatments lags behind and is an important area for future research
Thank you for your attention
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